CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-167

CHEMISTRY REVIEW(S)

Addendum to Chemist's Review #2

To: NDA 21-167; Chemist's Review #2
From: Michael Ortwerth, Ph.D.; Review Chemist /S/ 14-AUG-2000
Moo-Jhong Rhee, Ph.D.; Chemistry Team Leader /S/ 8/14/00
Re: Review of Labeling Amendment and Final draft PI and PPI labeling dated 02-AUG-2000 and 10-AUG-2000, respectively.
Date: 14-AUG-2000

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
AMENDMENT	02-AUG-2000	02-AUG-2000	10-AUG-2000
AMENDMENT	10-AUG-2000	10-AUG-2000	11-AUG-2000

RELATED DOCUMENTS:

Document Type	Document Date
Chemist's Review #1 for NDA 21-167	29-JUN-2000
Chemist's Review #2 for NDA 21-167	07-AUG-2000

Comments:

The above referenced documents contains the following:

Submission	Document Date	Contents
Amendment	02-AUG-2000	Amendment to Novartis' 26-JUL-2000 Response to FDA CMC IR Letter dated 29-JUN-2000. This document includes a replacement page 37 for the 26-JUL-2000 Amendment. This replacement page replaces the previously submitted Representation of Vivelle 0.025 mg/day printed backing to included the generic term for the drug product.
Amendment	10-AUG-2000	This document is the final draft labeling for the Physician Insert (PI) and Patient Package Insert (PPI) for Vivelle estradiol transdermal system.

SPONSOR'S STATEMENT (Amendment dated 02-AUG-2000):

"At this time we are providing an amendment to our July 26, 2000 response.

The attached page is provided as a replacement page 37 for the response. Page 37 of our July 26, 2000 response was a diagrammatic representation of the information that would appear on the printed backing of the 0.025 mg/day Vivelle transdermal systems. Although the diagram noted the tradename and the product strength, it did not note the generic term for the product. The generic term (estradiol transdermal) will also appear on the printed backing and the replacement diagram has been updated to reflect this."

REVIEWER'S COMMENTS:

The sponsor provided in Amendment 02-AUG-2000 a revision to the back panel labeling for the drug product. The new back panel includes the generic term "estradiol transdermal" to the printed backing. A copy of the representation for the Vivelle 0.025 mg/day printed backing is included as Attachment 1 of this Addendum.

REVIEWER'S EVALUATION: **Adequate**

SPONSOR'S STATEMENT (Amendment dated 10-AUG-2000):

"Attached is the draft and draft annotated label (Physician/Patient) for Vivelle (estradiol transdermal system) NDA 21-167. This draft label incorporates the revisions requested by the FDA at the August 3, 2000 labeling teleconference."

REVIEWER'S EVALUATION: The information provided in the draft labeling is **adequate.**

Conclusion:

From a chemistry, manufacturing, and controls viewpoint, all information contained in the sponsor's Amendments dated 02-AUG-2000 and 10-AUG-2000 are deemed **adequate** to support the approval recommendation for NDA 21-167 provided in Chemist's Review #2 dated 07-AUG-2000.

cc: HFD-510/Division File (NDA 21-167)
HFD-510/WKoch
HFD-580/MOrtwerth/MRhee/DMoore

APPEARS THIS WAY
ON ORIGINAL

1 page(s) of revised draft labeling has been redacted from this portion of the review.

DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #:	21-167	**DATE REVIEWED:**	07-AUG-2000
REVIEW #:	2	**REVIEWER:**	Michael Ortwerth

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
AMENDMENT	26-JUL-2000	28-JUL-2000	31-AUG-2000

NAME & ADDRESS OF APPLICANT:	Novartis Pharmaceuticals Corporation 59 Route 10 East Hanover, NJ 07936
DRUG PRODUCT NAME	
Proprietary:	Vivelle
Established:	Estradiol transdermal system
Code Name/#:	NA
Chem.Type/Rvw. Type:	5S; Type 6
PHARMACOL. CATEGORY/INDICATION:	Estrogen / Prevention of Postmenopausal Osteoporosis
DOSAGE FORM:	Patch, Extended Release
STRENGTHS:	0.025, 0.0375, 0.05, 0.075, or 0.1 mg/day
ROUTE OF ADMINISTRATION:	Transdermal; Patch
Rx/OTC:	X Rx __ OTC
SPECIAL PRODUCTS: (If yes, fill out the form for special products and deliver to TIA through team leader for data entry)	__ Yes X No

APPEARS THIS WAY
ON ORIGINAL

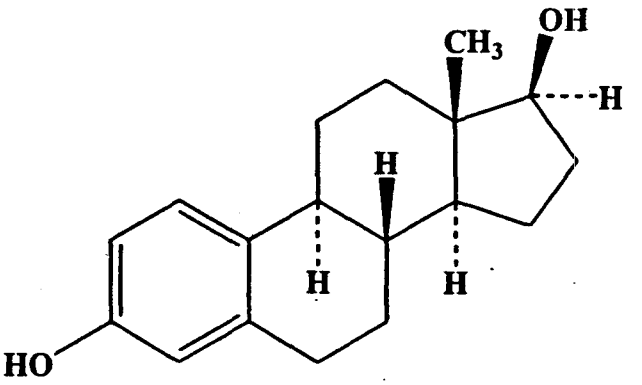
CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Estradiol

Chemical Name: Estra-1,3,5(10)-triene-3,17-diol, (17β)-

Compendial Name: Estradiol **CAS Registry Number:** [50-28-2]

Structural Formula:



Molecular Formula: $C_{18}H_{24}O_2$ **Molecular Weight:** 272.39

SUPPORTING DOCUMENTS: NDA 21-167 CMC Review #1 dated 29-JUN-2000

RELATED DOCUMENTS (if applicable): NA

CONSULTS: NA

REMARKS:

Amendment Submissions:

Document Date	Submission Contents
26-JUL-2000	Response to IR Letter dated 29-JUN-2000

This review covers the evaluation of information sent by the sponsor in response to the information request letter dated 29-JUN-2000.

The following attachments should be noted:

ATTACHMENT 1: Updated Drug Product Specifications; Issue Date: 20-JUL-2000
ATTACHMENT 2: Drug Product Stability Protocol and Stability Commitment
ATTACHMENT 2: Drug Product Stability Data: Lot 0B2402-A1; 0.05 mg/day Patch
ATTACHMENT 4: Representation of the Vivelle 0.025 mg/day printed backing and Actual Vivelle printed backing (for the 0.05 mg/day system, reflective of that for the 0.025 mg/day systems)

CONCLUSIONS & RECOMMENDATIONS:

From Chemistry Manufacturing and Controls point of view this NDA may be **APPROVED**.

/S/ 01-AUG-2000

Michael Ortwerth, Ph.D. Date
Review Chemist, HFD-580

/S/ 8/8/00

Moo-Jhong Rhee, Ph.D. Date
Chemistry Team Leader, HFD-580

cc:
Org. NDA 21-167
HFD-580/Division File
HFD-580/MOrtwerth
HFD-510/BKoch
HFD-580/DMoore
HFD-580/MRhee
R/D Init by: MRhee

filename: **N21167.002**

APPEARS THIS WAY
ON ORIGINAL

19 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

Go to Hyperlinked Table of Contents

NDA #: 21-167 **DATE REVIEWED:** 29-JUN-2000

REVIEW #: 1 **REVIEWER:** Michael Ortwerth

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	19-OCT-1999	20-OCT-1999	02-NOV-1999
AMENDMENT	06-MAR-2000	07-MAR-2000	17-APR-2000
AMENDMENT	15-JUN-2000	19-JUN-2000	19-JUN-2000

NAME & ADDRESS OF APPLICANT:

Novartis Pharmaceuticals Corporation
59 Route 10
East Hanover, NJ 07936

DRUG PRODUCT NAME

Proprietary:	Vivelle
Established:	Estradiol transdermal system
Code Name/#:	NA
Chem.Type/Rvw. Type:	5S; Type 6

PHARMACOL. CATEGORY/INDICATION: Estrogen / Prevention of Postmenopausal Osteoperosis

DOSAGE FORM: Patch, Extended Release

STRENGTHS: 0.025, 0.0375, 0.05, 0.075, or 0.1 mg/day

ROUTE OF ADMINISTRATION: Transdermal; Patch

Rx/OTC: _X_ Rx __ OTC

SPECIAL PRODUCTS: __ Yes _X_ No
(If yes, fill out the form for special products and deliver to TIA through team leader for data entry)

APPEARS THIS WAY
ON ORIGINAL

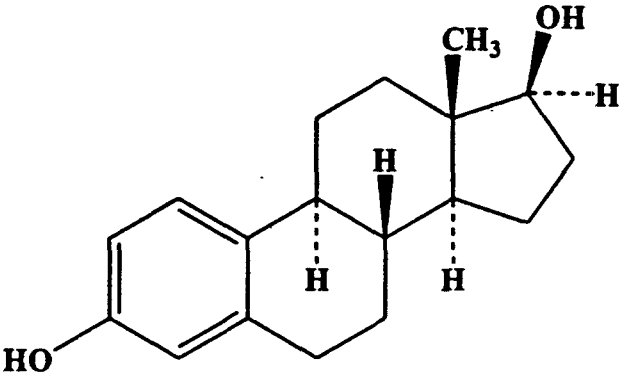
CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Apomorphine hydrochloride hemihydrate

Chemical Name: Estra-1,3,5(10)-triene-3,17-diol, (17β)-

Compendial Name: Estradiol **CAS Registry Number:** [50-28-2]

Structural Formula:



Molecular Formula: $C_{18}H_{24}O_2$ **Molecular Weight:** 272.39

SUPPORTING DOCUMENTS:

Type/ Number	Subject	Holder	Status	Review Date	Letter Date
DMF / —			**Adequate**	22-JUN-2000 OrtwerthM	NA
DMF/ —			**Adequate**[1]	04-JUN-1993 DaviesH NDA 20-323 Rev #1	NA
DMF/ —			**Adequate**	23-OCT-1998 MitraA	NA
DMF/ —			**Adequate**	08-MAY-2000 MitraA	NA
DMF/ —			**Adequate**[1]	04-JUN-1993 DaviesH NDA 20-323 Rev #1	NA
DMF/ —			**Adequate**	16-JUL-1997 MitraA	NA
DMF/ —			**Adequate**[1]	04-JUN-1993 DaviesH NDA 20-323 Rev #1	NA
DMF/ —			**Adequate**	23-OCT-1998 MitraA	NA

Type/ Number	Subject	Holder	Status	Review Date	Letter Date
DMF/ —			Adequate[1]	04-JUN-1993 DaviesH NDA 20-323 Rev #1	NA
DMF/ —			Adequate	16-JUL-1997 MitraA	NA

[1]These DMFs were reviewed in complete within CMC reviews 1-5 of NDA 20-323. As of the date of this review, no further updates have been made to these DMFs concerning the cross-referenced materials.

RELATED DOCUMENTS (if applicable):

The sponsor cross-references NDA 20-323, IND 40,773, DMF — (active pharmaceutical ingredient) and IND —— NDA 20-323 is Vivelle Estradiol Transdermal System (0.0375, 0.05, 0.075, or 0.1 mg/day).

CONSULTS: NA

REMARKS:

This NDA for Vivelle (estradiol transdermal system) is submitted for a labeling change to add a new indication for the prevention of postmenopausal osteoporosis.

Ciba Pharmaceuticals Corporation, now Novartis Pharmaceuticals Corporation, received FDA approval (NDA 20-323) for Vivelle® (estradiol transdermal system) providing delivery of 0.0375, 0.05, 0.075, or 0.1 mg/day on 29-OCT-1994 for the following indications:

- Treatment of moderate to severe vasomotor symptoms associated with menopause
- Treatment of vulval and vaginal atrophy
- Treatment of hypoestrogenism due to hypogonadism, castration, or primary ovarian failure.

The data in this NDA (21-167) is provided to demonstrate that continuous daily administration of Vivelle (0.025, 0.0375, 0.05, 0.075, or 0.1 mg/day) also is an effective, safe ERT regimen for the prevention of postmenopausal osteoporosis.

The Vivelle transdermal system is designed to release Estradiol continuously upon application to intact skin into the blood stream. The active ingredient, Estradiol, is synthesized by and supported by DMF ——

The drug product manufacturer is The drug product packaging facility is also Novartis Pharmaceuticals Incorporated will carton the pouched product and release the finished goods and pouch stock only. As stated in the Vivelle NDA 20-323 both Novartis Pharmaceuticals are approved as release facilities for the drug product.

Drug product patches proposed for marketing are to be manufactured in a two shapes - circle (0.025, 0.0375, 0.05 mg/day) and oval (0.075 and 0.1 mg/day). As of the date of this review, stability lots have been provided with — months real-time data for the 0.025 mg/day drug product patch. Stability lot data for the other doses has been submitted to the NDA 20-323 Annual Report.

Foreign Marketing History:
Vivelle marketing authorization was received from the Canadian Health Authority on January 4, 1996 and launched in Canada in May 1996. In Canada it is indicated for the relief of menopausal and postmenopausal symptoms occurring in naturally or surgically induced estrogen deficiency states.

Note: Menorest™ (estradiol transdermal system) is identical to Vivelle and is marketed by Rhone Poulenc Rorer outside the U.S. and Canada in postmenopausal osteoporosis as well as for treatment of patients with estrogen deficiency syndrome.

Amendment Submissions:

Document Date	Submission Contents
06-MAR-2000	List of DMFs cross-referenced to the NDA and a statement supporting the exclusion of Microbial Testing from the drug product release and shelf-life specifications.
15-JUN-2000	Submission of stability data for Lot 3A1401-A1 missing from original submission.

CONCLUSIONS & RECOMMENDATIONS:

This application is APPROVABLE pending the resolution of deficiencies found in the Draft Deficiency Letter of this review.

/S/

Michael Ortwerth, Ph.D.
Review Chemist, HFD-580

29-JUN-2000
Date

/S/

Moo-Jhong Rhee, Ph.D.
ChemistryTeam Leader, HFD-580

6/29/00
Date

cc:
Org. NDA 21-167
HFD-510/Division File
HFD-580/MOrtwerth
HFD-510/CSO/WKoch
HFD-580/MRhee
R/D Init by: MRhee

filename: **N21167.001.doc**

54 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application: NDA 21167/000
Stamp: 20-OCT-1999
Regulatory Due: 20-AUG-2000
Applicant: NOVARTIS PHARMS
59 RT 10
EAST HANOVER, NJ 079361080
Priority: 3S
Org Code: 510

Action Goal:
District Goal: 21-JUN-2000
Brand Name: VIVELLE (ESTRADIOL TRANSDERMAL SYSTEM)
Estab. Name:
Generic Name: ESTRADIOL TRANSDERMAL SYSTEM

Dosage Form: (TRANSDERMAL SYSTEM)
Strength: 0.025 MG/DAY

Application Comment: THE APPLICATION IS SUBMITTED FOR A NEW DOSE OF 0.025 MG/DAY FOR THE IDICATION OF MODERATE TO SEVERE VASOMOTOR SYMPTOMS ASSOCIATED WITH MENOPAUSE/PREVENTION OF POSTMENOPAUSAL OSTEOPOROSIS. [NOTE: 0.0375, 0.05, 0.75, AND 0.1 MG/DAY DOSES WERE APPROVED UNDER NDA 20-323 WITHOUT THE ADDED INDICATION OF PREVENTION OF POSTMENOPAUSAL OSTEOPOROSIS.; THIS APPLICATION (NDA 21-167) CROSS REFERENCES THE APPROVED NDA 20-323] (on 21-DEC-1999 by M. ORTWERTH (HFD-580) 301-827-4260)

FDA Contacts:
E. GALLIERS (HFD-510) 301-827-6429 , Project Manager
M. ORTWERTH (HFD-580) 301-827-4260 , Review Chemist
M. RHEE (HFD-580) 301-827-4237 , Team Leader

Overall Recommendation: ACCEPTABLE on 29-FEB-2000 by J. D AMBROGIO (HFD-324) 301-827-0062

Establishment: ———

DMF No: ——
AADA:
Responsibilities: ———
Profile: CSN
OAI Status: NONE
Estab. Comment: ——— (on 21-DEC-1999 by M. ORTWERTH (HFD-580) 301-827-4260)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	21-DEC-1999				ORTWERTHM
OC RECOMMENDATION	21-DEC-1999			ACCEPTABLE BASED ON PROFILE	EGASM

Establishment: 2416082
NOVARTIS PHARMA INC (CIBA)
OLD MILL RD
SUFFERN, NY 10901

DMF No:
AADA:
Responsibilities: FINISHED DOSAGE PACKAGER
Profile: TDP
OAI Status: NONE
Estab. Comment: CARTONING OF POUCHED PRODUCT AND RELEASE OF FINISHED GOODS AND POUCH STOCK ONLY. (on 21-DEC-1999 by M. ORTWERTH (HFD-580) 301-827-4260)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	21-DEC-1999				ORTWERTHM
OC RECOMMENDATION	21-DEC-1999			ACCEPTABLE BASED ON PROFILE	FERGUSONS

Establishment: ——

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

DMF No: AADA:
Responsibilities:

Profile: TDP OAI Status: NONE
Estab. Comment: (on 21-DEC-1999 by M. ORTWERTH (HFD-580) 301-827-4260)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	21-DEC-1999				ORTWERTHM
SUBMITTED TO DO	21-DEC-1999	10D			FERGUSONS
DO RECOMMENDATION	29-FEB-2000			ACCEPTABLE BASED ON FILE REVIEW	PFIGAROL
OC RECOMMENDATION	29-FEB-2000			ACCEPTABLE DISTRICT RECOMMENDATION	DAMBROGIOJ

Establishment:

DMF No: AADA:
Responsibilities:

Profile: TDP OAI Status: NONE
Estab. Comment: (on 21-DEC-1999 by M. ORTWERTH (HFD-580) 301-827-4260)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	21-DEC-1999				ORTWERTHM
SUBMITTED TO DO	21-DEC-1999	10D			FERGUSONS
DO RECOMMENDATION	19-JAN-2000			ACCEPTABLE BASED ON FILE REVIEW	PFIGAROL
OC RECOMMENDATION	19-JAN-2000			ACCEPTABLE DISTRICT RECOMMENDATION	DAMBROGIOJ

APPEARS THIS WAY
ON ORIGINAL